

Comments of the National Abortion Federation and Planned Parenthood Federation of America in Opposition to Citizen Petition and Request for Administrative Stay Regarding Mifeprex® (Mifepristone)

FDA Docket No. 02P-0377

The National Abortion Federation (“NAF”) and Planned Parenthood Federation of America (“PPFA”) submit these comments in opposition to the Citizen Petition and Request for Administrative Stay, Docket No. 02P-0377/CP1 (“Petition”) filed on August 20, 2002 and the responsive comments filed on October 10, 2003 (“Comments”) by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America (“Petitioners”). Petitioners allege, among other contentions, that the FDA-approved regimen for the administration of Mifeprex (mifepristone) is dangerous to women and that approval should be withdrawn.

NAF is the professional association of abortion providers in the United States and Canada; its members include some 400 nonprofit and private clinics, women’s health centers, and private physicians, as well as nationally and internationally recognized researchers, clinicians, and educators at major universities and teaching hospitals. PPFA is the world’s largest voluntary reproductive health care organization. Both NAF and PPFA are dedicated to serving the interests of women and to ensuring that American women’s access to safe and legal methods of abortion, including the Mifeprex regimen, remains intact.

NAF and PPFA submit these comments to correct several misstatements regarding the safety of Mifeprex made in the Petition and Comments. Petitioners contend that the FDA-approved Mifeprex regimen is unsafe because it does not require prescribers to use routine ultrasound and does not limit the distribution of Mifeprex to physicians who meet certain qualifications beyond those already delineated in the FDA-approved “Prescriber’s Agreement.”

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Petitioners also contend that FDA should withdraw the approval of Mifeprex because not all prescribers are following the dosing regimen described in the approved labeling.

Petitioners' contentions regarding the safety of Mifeprex are grounded in mischaracterizations of the standard of care in early pregnancy, and would advocate sharp departures from current norms in the practice of medicine. In evaluating the new drug application ("NDA") for Mifeprex, FDA properly considered the safety and effectiveness of the drug in the context in which it would be used, taking into consideration current standards of care. Accordingly, FDA properly concluded that Mifeprex can be provided safely and effectively in accordance with general practices in early pregnancy, and that providers who meet the qualifications set forth in the Prescriber's Agreement possess the necessary clinical expertise to provide Mifeprex safely and effectively to their patients. FDA's conclusions have been ratified by the post-approval history of safe and effective use of Mifeprex. The Petitioners present no sound scientific basis upon which FDA's approval should be withdrawn (*see* Parts I-III below).¹ Furthermore, FDA cannot grant the relief that Petitioners request with respect to providers' use of evidence-based regimens that differ from the FDA-approved regimen (*see* Part IV below).

I. FDA Correctly Concluded that Mifeprex May Be Safely Provided Without Mandatory Routine Ultrasound.

Petitioners, seemingly recognizing the weakness of their argument that Mifeprex cannot be provided safely and effectively under any circumstances, erroneously assert that Mifeprex can be provided safely and effectively only with the routine use of ultrasound to assess the gestation of pregnancy and rule out an ectopic pregnancy. (Petition at 5, 57-61; Comments at 14.) FDA

¹ As discussed in the Opposition of the Population Council, Inc and Danco, Inc., filed in this proceeding, the relief Petitioners seek is tantamount to the withdrawal of the NDA for Mifeprex. Such an action may not be taken as part (continued...)

carefully analyzed and ultimately rejected routine ultrasound when it approved Mifeprex for use in the United States. Petitioners' attempt to second-guess FDA's considered scientific judgment is without merit.

A. The Current Standard of Care Employs a Variety of Methods to Confirm and Date Pregnancy.

Petitioners argue that routine ultrasound is necessary for the safe use of Mifeprex. This assertion is not medically accurate. Health care providers throughout the United States and worldwide manage and diagnose pregnancies without the routine use of ultrasound. While safe provision of medical abortion requires accurate pregnancy dating and follow-up care, clinicians can and do evaluate early pregnancy in a variety of health care settings using an array of approaches other than ultrasound. Elements of such evaluations include patient history, physical examination, and pregnancy testing. Ultrasound is useful in some cases, but is not necessary as a routine matter.

Patient history is the starting point for assessing gestational age. Women often can state with certainty the onset of their last menstrual period ("LMP"). For example, in a study of mifepristone-misoprostol abortion, 798 of 799 women stated an exact date for LMP.² Dating by LMP agreed precisely or within 1 week of physicians' estimates based on clinical parameters 52.6% and 92.4% of the time, respectively.³

of a response to a Citizen Petition, and the stay requested by Petitioners is not supported by the criteria set forth in FDA's regulations. See 21 U.S.C. § 355(e), 21 C.F.R. § 10.35.

² Charlotte Ellertson et al., "Can women use medical abortion without medical supervision?" Reprod Health Matters 1997; 9:149-161.

³ Id. at 152. Eight women (1.0%) underestimated the duration of pregnancy by 2 weeks, 1 (.01%) underestimated by 3 weeks, and 2 (0.3%) underestimated by 4 weeks. Overall complete abortion rates ranged from 88% to 93%. Id.

In addition to patient history, physical examination plays an important role in confirming a diagnosis of pregnancy and estimating gestational age.⁴ Enlargement of the uterus begins shortly after implantation. After approximately 4 weeks' gestation, the size of the uterus increases about 1 cm per week.⁵ Consequently, during the first trimester, a pelvic bimanual examination can provide a good estimate of gestational age, particularly if uterine sizing concurs with a reliable dating of LMP.⁶

Furthermore, clinical laboratory testing for the presence of hCG in blood or urine provides a simple, inexpensive, and reliable method for diagnosing and assessing pregnancy.⁷ Mean serum β -hCG levels are closely correlated with gestational age during early pregnancy. Pregnant women whose β -hCG levels are less than 5000 mIU/mL are unlikely to be at greater than 6 weeks' gestation.⁸

Thus, patient history, physical examination, and hCG laboratory testing offer clinicians a variety of methods for establishing gestational age among women requesting early medical abortion. Because the routine use of ultrasound is not necessary for assessing early pregnancy, it is not the current standard of care in obstetrics, either in or outside of the abortion context.⁹

⁴ Maureen Paul et al., "The roles of clinical assessment, human chorionic gonadotropin assays, and ultrasonography in medical abortion practice," 183 Medical Abortion Supplement to the American Journal of Obstetrics and Gynecology S34 (Aug. 2000).

⁵ Id. at S35.

⁶ Id.

⁷ Steven R. Goldstein et al., "Documenting Pregnancy and Gestational Age," in Maureen Paul et al. (eds.), A Clinician's Guide to Medical and Surgical Abortion at 41. Philadelphia, PA: Churchill Livingstone, 1999.

⁸ Maureen Paul et al., supra n.4 at S36.

⁹ See, e.g., American Academy of Family Physicians, Management of Maternity Care, at 7, 16, available at <http://www.aafp.org/x3390.xml> ("...diagnosis of pregnancy can be reached based on a combination of subjective symptoms, objective signs, and laboratory results.... Routine use of ultrasound ... is not recommended").

The Petitioners also err in stating that NAF's standards of care require the routine use of transvaginal ultrasound to assess gestation. (Petition at 59-60.) NAF creates evidence-based clinical policy guidelines that are developed by consensus based on rigorous review of current medical literature and known patient outcomes. Neither NAF's *Clinical Policy Guidelines*¹⁰ nor NAF's "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion" call for routine ultrasound examination for gestational assessment for medical abortion. Rather, NAF's standards recommend that, if the physical exam and LMP are substantially discordant, ultrasound be used to confirm and document gestational age.¹¹ NAF's standards describe routine ultrasound only as an option that is available to clinicians.¹² This standard is reflective of evidence-based practice both in the United States and elsewhere.¹³

In addition, mifepristone was developed, studied in clinical trials, and approved for early abortion in Europe without the use of routine ultrasound.¹⁴ In France, where mifepristone has

¹⁰ Available at www.guidelines.gov.

¹¹ National Abortion Federation, *Clinical Policy Guidelines 2004*, at 7.

¹² *Id.*

¹³ NAF's "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion" states "Transvaginal probe or abdominal probe ultrasound *may be used* routinely to confirm gestational age and intrauterine gestation. Transvaginal probe ultrasound is preferable because it detects pregnancy about one week earlier than abdominal probe ultrasound. *If ultrasound examination is performed*, document findings (gestational age, yolk sac, embryonic pole, presence of cardiac activity) for the medical record before administering mifepristone." [Emphasis added]. The Protocol also notes that while researchers in the United States utilized routine ultrasound in the investigation of mifepristone, experienced medical abortion providers in other countries do not rely on routine sonography. The Protocol concludes "high efficacy and safety results in the French trials suggest that this selective use of sonography suffices when medical abortion is provided by experienced clinicians." National Abortion Federation, *Early Medical Abortion with Mifepristone and Other Agents: Overview and Protocol Recommendations*, Washington, DC: 2002.

¹⁴ Elizabeth Aubeny *et al.*, "Termination of early pregnancy (up to and after 63 days amenorrhea) with mifepristone (RU 486) and increasing doses of misoprostol," *Int J Fertil* 1995; 40 (Supplement 2): 85-91.

been registered since 1988, mifepristone abortions do not involve the routine use of ultrasound.¹⁵ The efficacy and safety results from the French experience with mifepristone¹⁶ demonstrate that routine use of ultrasound is not necessary to ensure safe provision of Mifeprex.¹⁷

B. Routine Ultrasound Use is Not Necessary to Rule Out Ectopic Pregnancy.

Petitioners' claims that routine ultrasound is necessary to detect an ectopic pregnancy (Petition at 60; Comments at 14) are also not supported by the medical literature and are inconsistent with current standards of care for the management of early pregnancy, regardless of whether the woman continues the pregnancy or has an abortion.

First, medical abortion does not increase the risk of an ectopic pregnancy.¹⁸ In fact, women who seek early abortion care have a lower rate of ectopic pregnancy than the general population.¹⁹

Second, clinicians diagnose ectopic pregnancy using a variety of tools, including β -hCG assays, radioimmunoassays for progesterone, laparoscopy, and sonography.²⁰ β -hCG assays are

¹⁵ Mitchell D. Creinin & Elizabeth Aubeny, "Medical Abortion in Early Pregnancy," in Maureen Paul et al. (eds.), A Clinician's Guide to Medical and Surgical Abortion at 99. Philadelphia, PA: Churchill Livingstone, 1999.

¹⁶ See generally Mitchell D. Creinin, "Medical abortion regimens: Historical context and overview," 183 Medical Abortion Supplement to the American Journal of Obstetrics and Gynecology at S4-S6 (Aug. 2000).

¹⁷ Indeed, no studies have ever evaluated whether routine use of ultrasound for evaluation of gestational age in medical abortion improves clinical outcomes. One study did attempt to evaluate whether routine ultrasound use would be clinically relevant. This study showed that clinicians felt certain that an ultrasound would not have been needed to confirm the gestational age in 60%, 66%, and 46% of women ≤ 42 days, 43-49 days, and ≥ 50 days, respectively. Stephen L. Fielding et al., "Clinicians' perception of sonogram indication for mifepristone abortion up to 63 days," Contraception 2002;66:27-31.

¹⁸ See FDA, CDER, Mifepristone Questions and Answers, available at www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm (April 17, 2002).

¹⁹ Jerry Edwards & Mitchell D. Creinin, "Surgical abortion for gestations of less than 6 weeks," Curr Probl Obstet Gynecol Fertil 1997; 20: 11-19.

²⁰ Lee P. Shulman et al., "Management of Abnormal Pregnancies," in Maureen Paul et al. (eds.), A Clinician's Guide to Medical and Surgical Abortion at 162. Philadelphia, PA: Churchill Livingstone, 1999.

particularly effective because the mean doubling time of serum β -hCG in a normal intrauterine pregnancy is known to be 1.40-1.98 days, whereas in patients with an ectopic pregnancy, β -hCG typically rises at a much slower rate.²¹ Physical exam, patient history, and assessment of the patient's symptoms also may aid in detecting an ectopic pregnancy.²²

When a clinician suspects an ectopic pregnancy because of patient symptoms, physical examination findings, or laboratory test results, ultrasound may be indicated to confirm the ectopic pregnancy.²³ Under the approved Mifeprex labeling, if a provider considering Mifeprex for a patient determines that an ultrasound examination is necessary, the provider can either perform the ultrasound examination, or if unable to do so, can refer the patient to a practitioner who can provide this service. This is the same standard that applies to any health care provider who suspects that his or her patient has an ectopic pregnancy.²⁴ To require more for health care providers prescribing Mifeprex is medically unjustified and would border on improper regulation

²¹ Id. Because the interassay variability of β -hCG is 10-15%, a change of less than 15% is evidence of a plateau, and plateaued levels of β -hCG are predictive of ectopic pregnancy. Id.

²² Petitioners' misrepresentations regarding the detection of an ectopic pregnancy are not surprising given that Petitioners wrongly assess the treatment options for ectopic pregnancies. Petitioners incorrectly assert that emergency surgery is the only treatment option for women suffering from an ectopic pregnancy. (Petition at 61.) In fact, numerous studies dating to the early 1980s have demonstrated the safety and efficacy of methotrexate as a nonsurgical treatment for ectopic pregnancy. Toshinobu Tanaka et al., "Treatment of interstitial ectopic pregnancy with methotrexate: report of a successful case," Fertil Steril 1982;37:851-2; Thomas G. Stovall et al., "Outpatient chemotherapy of unruptured ectopic pregnancy," Fertil Steril 1989;51:435-8.; Thomas G. Stovall et al., "Single-dose methotrexate for treatment of ectopic pregnancy," Obstet Gynecol 1991;77:754-7. Reported success rates, defined as resolution without surgical intervention, range from 67% to 100% with a median of 84% for the single-dose methotrexate regimen. ACOG Practice Bulletin, Medical Management of Tubal Pregnancy, Clinical Management Guidelines for Obstetrician-Gynecologists, 3:1998 at 3. Non-surgical treatment for ectopic pregnancy has obvious benefits for patients, including the preservation of future fertility.

²³ See, e.g., American Academy of Family Physicians, Management of Maternity Care, at Appendix B (available at <http://www.aafp.org/x3393.xml>).

²⁴ See, e.g., id. at 30, Appendix B.

of the practice of medicine. Notably, such a requirement would also create a significant obstacle to providing medical abortion, especially in rural areas.

In short, there is no rational reason for requiring universal ultrasound prior to prescribing Mifeprex. Because routine ultrasound is not the standard of care for all confirmed pregnancies, there is no reason to impose such a requirement only for Mifeprex. FDA correctly rejected an ultrasound requirement, and Petitioners present no scientific basis for reconsidering that determination.

II. FDA's Requirements for Mifeprex Providers Are Sufficient to Assure Safe Use.

The Prescriber's Agreement for Mifeprex requires providers ordering Mifeprex to certify that they meet certain qualifications. These qualifications include (1) the ability to assess the duration of pregnancy accurately; (2) the ability to diagnose ectopic pregnancies; (3) the ability to provide or arrange for surgical intervention in the event of an incomplete abortion or severe bleeding; and (4) the ability to assure the patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. The Agreement's stipulation that the provider be able to assess gestational age and diagnose ectopic pregnancies is consistent with the standards of care in the United States for treatment of early pregnancy, as discussed above. Likewise, the ability to refer a woman to another physician or surgeon where necessary for the management of a complication represents standard medical practice.²⁵ In adopting these standards, FDA set forth qualifications and stipulations that would safeguard the health of women without intruding excessively in the practice of medicine.

²⁵ See, e.g., *id.* at 30.

Petitioners, by contrast, contend that FDA should impose certain additional burdensome restrictions on the distribution of Mifeprex that would interfere directly and substantially with the practice of medicine. Petitioners argue that FDA should require that Mifeprex providers be trained in surgical abortion, have admitting privileges to emergency facilities within an “objective geographical limitation” (presumably some mandatory maximum distance from the provider’s place of business), and that Mifeprex prescribing be restricted to physicians only. (Petition at 65; Comments at 14-15.) FDA considered and then rejected these restrictions prior to approving Mifeprex. Petitioners nonetheless argue that FDA was wrong in approving Mifeprex without these restrictions, and that, without them, Mifeprex cannot be provided safely. The data do not support the Petitioners’ claims.

A. Physicians Need Not Be Trained in Surgical Abortion to Provide Mifeprex Safely.

Petitioners argue that Mifeprex should be provided only by “properly trained” physicians. (Petition at 62; Comments at 14-15.) Petitioners describe “properly trained” as including training in surgical abortion (Petition at 62-63),²⁶ but this description is unfounded. NAF and PPFA agree that proper training is critical in the provision of safe abortion services, as with any medical procedure. NAF guidelines state that abortion providers must receive training,²⁷ and PPFA’s Standards require that clinicians be trained and have demonstrated

²⁶ Petitioners stress that, prior to approving Mifeprex, FDA considered imposing a requirement that Mifeprex prescribers complete “training certified by the distributor” (Petition at 52). FDA correctly rejected this proposed requirement, which would have imposed stricter restrictions upon Mifeprex than other medications, including those with a less well-established safety record. Like FDA, most European countries have not mandated training curricula for the use of mifepristone. See letter from Danielle Hassoun, Director, Center for Training in Reproductive Health Technologies, Paris, France, to NAF (March 31, 2004).

²⁷ NAF’s Clinical Policy Guidelines state, “[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention, recognition, and management of complications.” Clinical Policy Guidelines 2004 at 1.

competence in the provision of medical abortion.²⁸ However, Petitioners are incorrect in arguing that providers of Mifeprex must be trained in *surgical* abortion.

Petitioners hyperbolize that training in surgical abortion is necessary because of the “high failure rate” of Mifeprex. (Petition at 63.) In fact, in only about 5% of cases will women choosing early abortion with Mifeprex need surgical intervention to complete the abortion.²⁹ More specifically, surgical abortion is strongly recommended only in the approximately 1% of cases where the Mifeprex/misoprostol regimen does not produce an abortion and the pregnancy continues. In the other approximately 4% of cases, surgical intervention is indicated for reasons such as prolonged or heavy bleeding or patient preference.³⁰ In such cases, the FDA-approved labeling provides that, if the Mifeprex provider does not provide surgical intervention himself or herself, the patient will be referred to another provider for that treatment.³¹ This standard reflects common medical practice.³² To require more, as Petitioners suggest, would represent an

²⁸ “The Physician Director must be trained in medical abortion.” PPFA Manual of Medical Standards and Guidelines, at 1; “Clinicians providing medical abortion services must... [b]e appropriately trained and experienced with demonstrated skills in the provision of medical abortion.” Id. at 2. Health care providers have flexibility in training methods and materials to ensure that individual clinical needs are addressed. Numerous educational opportunities and resources exist for new providers of medical abortion. NAF has developed a series of educational materials regarding medical abortion for health care professionals, including several ACCME-accredited continuing medical education programs. These materials can be accessed at www.earlyoptions.org.

²⁹ James G. Kahn et al., “The efficacy of medical abortion: A meta-analysis,” Contraception 2000; 61: 29-40.

³⁰ Id.

³¹ The Prescriber’s Agreement states “Under federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications: ... [a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.” Available at <http://www.fda.gov/cder/drug/infopage/mifepristone/prescriberagreement.pdf>.

³² “There must be arrangements for appropriate back up for surgical referral and emergency.” PPFA Manual of Medical Standards and Guidelines, at 1. NAF’s protocol states “Delivery of all abortion services requires twenty-four hour availability of a clinician for assessment of potential complications. This is especially critical with medical abortion where the timing of bleeding may be less predictable and heavy or persistent bleeding may occur at home and require evaluation. Surgical aspiration, administration of uterotonic agents, and, rarely, intravenous fluid (continued...) ”

unreasonable and unnecessary intrusion into the practice of medicine. By Petitioners' logic, cardiologists should no longer be able to treat patients because they are not trained in open heart surgery, and midwives should not be able to provide obstetric care because they do not perform cesarean sections. Petitioners' position is plainly unreasonable.

Petitioners also suggest that because surgical abortion is the back-up for an incomplete or failed medical abortion, medical abortion cannot be provided in geographic areas where surgical abortion is not offered. (Petition at 10, nn. 28, 62.) Again, this suggestion fails to consider the standard of care in comparable medical situations. Medical abortions with Mifeprex are medically comparable to spontaneous abortions.³³ Numerous facilities and health care providers that do not provide surgical abortion manage spontaneous abortions surgically, and can and do provide surgical intervention in the event of heavy bleeding or an incomplete medical abortion.³⁴ A recent study documents that spontaneous abortion accounts for 26.3% of women hospitalized as a result of a pregnancy loss.³⁵ Petitioners ignore the reality of obstetrical practice in alleging that clinicians who do not provide surgical abortion cannot assure that appropriate surgical intervention will be available in the small percentage of situations where it is necessary.

administration or blood transfusion may be necessary for treatment of incomplete abortion with excessive bleeding. Those providers who do not perform surgical aspiration completion should secure a formal arrangement for surgical back-up." Protocol at 39.

³³ ACOG Practice Bulletin, Medical Management of Abortion, Clinical Management Guidelines for Obstetrician-Gynecologists, 26: April 2001 at 4.

³⁴ Surgical intervention techniques used to treat heavy uterine bleeding, incomplete medical abortion, and spontaneous abortion include dilation and curettage ("D&C") and suction aspiration. While these two procedures can be used also for elective surgical abortion, a provider need not provide elective surgical abortions to be capable of providing D&C or suction aspiration for other indications.

³⁵ H. Joanna Jiang et al., Care of Women in U.S. Hospitals, 2000. HCUP Fact Book No. 3. AHRQ Publication Number 02-0044, October 2002. Agency for Healthcare Research and Quality, Rockville, MD. Available at <http://www.ahrq.gov/data/hcup/factbk3.htm>).

B. Physicians Do Not Need Admitting Privileges to Provide Mifeprex Safely.

Petitioners also contend that FDA's decision not to require physicians to have admitting privileges to emergency facilities was improper and suggest that an "objective geographical limitation" is necessary. (Petition at 65; Comments at 14-15.) Again, Petitioners are mistaken. Such a requirement would have no bearing on patient safety, for in the event of a medical emergency, it is of paramount importance that the patient, not the physician, be able to access emergency care quickly. Moreover, current standards of medical care do not mandate either that physicians treating other medical conditions have admitting privileges or that admitting privileges be within an "objective geographical limitation." It is common practice for a hospital emergency department to have on-call staff that can assist the patient if her physician does not have admitting privileges at that hospital. In addition, in some communities, hospitals do not grant admitting privileges to physicians. Instead, these hospitals have physicians on staff who admit the patients.

Petitioners also imply that dispensing and administration of Mifeprex should be limited by FDA to *physicians* meeting the restrictive qualifications discussed above.³⁶ Such a restriction would represent a direct and unnecessary intrusion into the states' traditional ability to regulate the practice of medicine. Individual state laws and practice acts establish the permitted scope of practice for all licensed health care providers, and in many states, health care professionals other than physicians safely prescribe and dispense prescription medications. Moreover, in at least three states, health care professionals other than physicians - such as physician assistants,

³⁶ Petition at 50-55, 68.

certified nurse midwives, and nurse practitioners - are authorized to provide medical abortion.³⁷

Whether non-physicians in additional states may dispense Mifeprex for medical abortion is a question of state law. Thus, with regard to Mifeprex, the Agency has stated:

Some states allow physicians to supervise other health care practitioners, such as certified registered nurse practitioners and nurse midwives, and these states may allow a supervised health care provider to dispense mifepristone. Health care providers should check their state law provisions.³⁸

Petitioners' suggestion that FDA intervene in this area of traditional state regulation is inappropriate.³⁹

In sum, FDA, in possession of all of the scientific data reflecting the experiences of thousands of women taking Mifeprex, properly rejected additional qualifications such as those proposed by the Petitioners as medically unnecessary. These additional qualifications would represent an unprecedented and unjustifiable intrusion into the practice of medicine and would only serve to curtail women's ability to access this safe early abortion option. Petitioners make the unfounded assertion that the absence of additional restrictions has caused adverse events described in a "Dear Doctor" letter. (Petition at 6, 65-71.) FDA has reviewed the adverse events

³⁷ See e.g. Ca. Bus. & Prof. Code § 2253; 2001 Conn. AG LEXIS 26 (July 2001); Armstrong v. State, 989 P.2d 363 (Mont. 1999).

³⁸ See FDA, Mifepristone Questions and Answers, available at <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa.htm>.

³⁹ See Hillsborough County, Fl. v. Automated Med. Labs., 471 U.S. 707, 715 (1985) (in matters related to health and safety, there is a presumption against federal preemption of state regulation under the Supremacy Clause of the Constitution).

described in that letter and has concluded that a causal relationship between the use of Mifeprex and the adverse events has not been established.⁴⁰

III. Mifeprex Is Safe for Women.

The Petition's repeated assertion that Mifeprex is unsafe is inconsistent with the studies that supported FDA's approval, other published medical studies, and the experience of medical practitioners who have provided Mifeprex to patients throughout the world.⁴¹ (Comments at 18, n.18.) In fact, Mifeprex is safer and more effective than surgical abortion for some women.

A. The Pre- and Post-Approval Data Establish Mifeprex's Safety and Effectiveness.

Prior to FDA's approval of Mifeprex, more than 2,000 women participated in clinical trials in the United States. Contrary to Petitioners' contentions otherwise, these studies demonstrated the safety and effectiveness of Mifeprex, used in conjunction with misoprostol, up to 49 days' gestation.⁴² (Comments at 2.) Those results confirmed the experience of two trials previously conducted in France.⁴³ Moreover, research completed since the French trials has

⁴⁰ FDA, CDER, Mifepristone Questions and Answers, available at www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm (April 17, 2002).

⁴¹ Mifepristone has been approved for use in 29 countries including major European countries and the United States.

⁴² Irving M. Spitz *et al.*, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338(18) *New Eng J. Med.* 1241-47 (1998); Beverly Winikoff *et al.*, "Acceptability and Feasibility of Early Pregnancy Termination by Mifepristone-Misoprostol: Results of a Large Multicenter Trial in the United States," 7 *Archives of Family Medicine* 360-66 (1998).

⁴³ Remi Peyron *et al.*, "Early Termination of Pregnancy with Mifepristone (RU486) and Orally Active Prostaglandin Misoprostol," 328 *New Eng J. Med.* 1509-13 (1993); Elizabeth Aubeny *et al.*, "Termination of early pregnancy (up to 63 days amenorrhea) with mifepristone and increasing doses of misoprostol," *Int. J. Feteril. Menopausal Stud.* 1995; 40 Suppl. 2:85-91. The Petitioners claim that these trials were inadequate because they were not blinded or randomized. It is not possible to blind either health care providers or women to treatment either with surgical abortion or medical abortion. There have only been two studies that have randomized women to surgical or medical abortion. *See, e.g.*, Mitchell D. Creinin, "Randomized comparison of efficacy, acceptability and cost of medical versus surgical abortion," *Contraception* 2000;62:117-24; R. C. Henshaw *et al.*, "Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment," *BMJ* 1993; 307:714-7. Both studies had very low enrollment (n=50 and n= 195, respectively) because few women truly have no preference for one method or the other, and thus few women can ethically be randomized.

demonstrated that Mifeprex is safe and effective in terminating early pregnancy up to 63 days' gestation when used with vaginal misoprostol.⁴⁴

In the more than a decade since it was first licensed, nearly one million women worldwide, excluding China, have used Mifeprex for ending early pregnancy.⁴⁵ In 2002, it was estimated that an additional 15 million mifepristone abortions had been conducted in China in the previous decade.⁴⁶ Since the FDA's approval of Mifeprex in 2000, more than 250,000 American women have used Mifeprex to terminate an early pregnancy.⁴⁷ This experience has confirmed that Mifeprex is safe for women.⁴⁸

Petitioners point to adverse events reported since the approval of Mifeprex to support their contention that the approval should be withdrawn. As illustrated in the response of Danco Laboratories, LLC to the Petition, FDA has evaluated the reported adverse events and concluded that none of those events showed that Mifeprex is unsafe for women.⁴⁹ FDA has stated that "it is

⁴⁴ Eric A. Schaff et al., "Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days," Contraception 2000;61:41-6.

⁴⁵ Danco Laboratories Press Release, "More than 100,000 Women Have Chosen Mifeprex for Their Non-Surgical Abortion" (Sept. 24, 2002).

⁴⁶ Rosa Zhou et al., "Medical Abortion in China: A Fact Finding Mission," Critical Issues in Reproductive Health. New York: The Population Council, 2002.

⁴⁷ Danco Laboratories, "Mifeprex Fact Sheet" (March 2004).

⁴⁸ Richard Hausknecht, "Mifepristone and misoprostol for early medical abortion; 18 months experience in the United States," 2003 Contraception; 67:463-5.

⁴⁹ Population Council Opp. at 12-13; FDA, CDER, Mifepristone Questions and Answers, available at www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm (April 17, 2002). The "Dear Doctor" letter was issued by FDA before the death of Holly Patterson in September 2003. PPFA and NAF note that the Coroner's Report contradicts Petitioners' assertion about retained fetal tissue. In addition, Petitioners' allegation that emergency room staffs cannot manage Mifeprex patients who present to them is absurd. As discussed in the text, medical abortions with Mifeprex are medically comparable to spontaneous abortions, which emergency room physicians manage competently and safely.

unknown whether there is a causal relationship between any of the [adverse] events and the use of Mifeprex.”⁵⁰ Petitioners provide no evidence that would alter FDA’s conclusion.

Petitioners also argue that the adverse event reporting on Mifeprex has been “spotty” and question “whether individual lawful distributors of Mifeprex, who tend to be outside the mainstream pharmaceutical wholesale distribution industry will routinely report adverse events to FDA.” (Comments at 18.) There is simply no support for these allegations. Moreover, the Prescriber’s Agreement specifically requires the reporting of any hospitalization, transfusion, or other serious event, and there is no basis for the suggestion that prescribers are violating the agreement. Even more absurdly, Petitioners contend that distributors of Mifeprex outside “the lawful channels of distribution are even less likely to report adverse events.” (Comments at 18, n.93.) The implications of this argument are ridiculous. There is no drug for which the same cannot be said. That unlawful distributors are unlikely to report adverse events is not a legitimate ground for FDA to rescind approval of all prescription drugs.

B. Mifeprex Is Safer and More Effective Than Other Abortion Methods for Some Women.

The Petitioners also distort medical fact when it claims that Mifeprex provides no therapeutic benefit over surgical abortion. (Petition at 21-23; Comments at 4, 9.) Indeed, Mifeprex provides a clear benefit over surgical abortion methods for some women.

First, many women have a clear preference for medical abortion over surgical abortion. Studies have documented that even among women who require a surgical intervention to

⁵⁰ FDA, CDER, Mifepristone Questions and Answers, available at www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm (April 17, 2002).

complete their medical abortion, the vast majority would choose to use Mifeprex again if needed, and an even larger majority would recommend the method to others.⁵¹ Women who have chosen medical abortion prefer the Mifeprex regimen for many reasons, not the least of which is that it is noninvasive and allows them to avoid surgery.⁵² Although surgical abortion is very safe, it involves surgery, along with the risks of anesthesia, as well as the possibility (although remote) of the complications that can occur in all invasive surgical procedures.⁵³

Furthermore, some women have conditions that make a medical abortion preferable. This would include women with vaginal scarring, large uterine fibroids, certain abnormalities of the uterus or cervix, or obesity.⁵⁴ For example, if a woman suffers from uterine fibroids, surgical abortion can be technically difficult because the fibroids can obstruct or distort the cervix or uterus. Medical abortion, using the Mifeprex regimen, may be a preferable option for such women.⁵⁵

The Petitioners wrongly assert that because a small percentage of women undergoing medical abortion will require surgical treatment, “any patient who would be intolerant of surgical abortion, if such a class of patient exists, cannot use the Mifeprex Regimen.” (Petition at 23.) Women choosing medical abortion may be intolerant of surgical abortion as a first course of

⁵¹ Beverly Winikoff *et al.*, “Acceptability and Feasibility of Early Pregnancy Termination by Mifepristone-Misoprostol: Results of a Large Multicenter Trial in the United States,” at 360-66; Beverly Winikoff *et al.*, “Safety, Efficacy, and Acceptability of Medical abortion in China, Cuba, and India: A comparative trial of mifepristone-misoprostol versus surgical abortion,” 176 *Am. J. Obstet Gynecol.* 431-437 (1997).

⁵² Winikoff, “Acceptability and Feasibility of Early Pregnancy Termination by Mifepristone-Misoprostol: Results of a Large Multicenter Trial in the United States,” at 362.

⁵³ Claude J. Aguiillaume & Louise B. Tyrer, “Current Status and Future Projections on Use of RU-486,” *Contemporary OB/GYN*, 40(6), 23-40.

⁵⁴ Lynn Borgatta *et al.*, “The Challenging Abortion,” in Maureen Paul *et al.* (eds.), *A Clinician’s Guide to Medical and Surgical Abortion* at 169-76. Philadelphia, PA: Churchill Livingstone, 1999.

⁵⁵ *Id.*

treatment, and yet still agree to undergo a surgical procedure should the need for one arise during the course of a medical abortion. Indeed, because the administration of the Mifeprex regimen softens the cervix, it can facilitate the surgical procedure for these patients in the rare instances where surgery becomes necessary.

IV. Evidence-Based Alternative Regimens Do Not Contravene the FDA Approval.

The Petitioners also contend that offering the Mifeprex regimen through 63 days' gestation and permitting patients to administer the dose of misoprostol at home rather than requiring them to return to the medical office violates FDA's approval. (Petition at 71-75; Comments at 14, 18, 19-20.) Nothing in the FDA approval of Mifeprex, however, obligates providers to follow any specific dose or regimen for prescribing Mifeprex. The use of evidence-based, or "off-label," alternative regimens is an accepted part of standard medical practice if supported by published literature or other appropriate scientific evidence. Indeed, the published literature demonstrates that the alternative regimens about which the Petitioners complain are safe and effective. These alternatives may be more effective and have fewer side effects than the FDA-approved regimen.

Evidence-based, or "off-label," use occurs when a medical provider uses a medication in a way that differs from the FDA-approved label, but is based on published literature or other sources of authoritative scientific evidence.⁵⁶ As Petitioners concede (Petition at 46), it is "common" for physicians to use FDA-approved drugs in doses or contexts that were not

⁵⁶ William L. Christopher, "Off-Label Drug Prescription- Filling the Regulatory Vacuum," 48 Food & Drug L.J. 247, 248 (1993); Kaspar J. Stoffelmayr, "Products Liability and "Off-Label" Uses of Prescription Drugs," 63 U. Chi. L. Rev. 275, 277 (1996).

specifically approved by FDA so long as the alternative use is supported by adequate study.⁵⁷

Moreover, off-label use is an integral part of the discovery of new, effective drug therapies, which can often occur through serendipitous means.⁵⁸

The alternative regimens about which Petitioners complain - offering the medical abortion regimen through 63 days' gestation (rather than 49 days, as described in the approved labeling) and permitting patients to administer the dose of misoprostol at home rather than requiring them to return to the medical office - are appropriate uses of evidence-based medicine. In published study after published study, the safety and effectiveness of both of these alternative regimens have been well established. These studies indicate that, in some cases, these regimens achieve superior efficacy with fewer side effects than the FDA-approved regimen. For example, the home administration of vaginal misoprostol has repeatedly been found to be safe and

⁵⁷ It has been estimated that almost half of the United States population currently is taking a medication for an unlabeled indication or in an unlabeled manner. Veronica Henry, "Off-Label Prescribing Legal Implications," 20 J. Legal Med. 365, 365 (1999) (citing Lipman, Using Approved Drugs for Unapproved Purposes, Consumer Rep. Health, Feb. 1998, at 10). While estimates vary about the total number of prescriptions written that call for off-label use, an American Medical Association ("AMA") official has estimated that 40-60% of all prescriptions in the United States are written for off-label uses. Id.; Kaspar J. Stoffelmayr, supra n.56 at 278 (citing Fran Kritz, FDA Seeks to Add Drugs' New Uses to Labels, Wash. Post Health 11 (Mar. 29, 1994)); see also James M. Beck & Elizabeth D. Azari, "FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions," 53 Food & Drug L.J. 71, 80 (1998) (reporting that off-label prescriptions may account for more than 25% of the 1.6 billion prescriptions each year, with some estimates running as high as 60%).

⁵⁸ William L. Christopher, supra n.56 at 249; 12 FDA Drug Bulletin 4 (1982) ("Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations.").

effective.⁵⁹ Moreover, these same studies have shown that home administration is acceptable to patients who have used the regimen, and is no less safe than the FDA-approved regimen.⁶⁰

Similarly, Mifeprex regimens involving the use of vaginal misoprostol have been demonstrated to be safe and effective through 63 days' gestation.⁶¹ Studies involving these regimens in women up to 63 days' gestation have achieved overall efficacy of up to 99%, which is superior to the efficacy shown in the U.S. and French trials on which the FDA approval was based (92.1% and 95%, respectively). Compared to regimens using 400 µg oral misoprostol, regimens using 800 µg vaginally have fewer gastrointestinal side effects and can shorten the medical abortion process.⁶²

Nothing about FDA's approval of Mifeprex is contrary to the general rule that off-label, or evidence-based, uses are appropriate medicine when supported by sufficient scientific studies. The Prescriber's Agreement that physicians must execute requires signing physicians to certify that they possess various qualifications and will adhere to certain procedural steps.⁶³ None of

⁵⁹ See, e.g., Eric A. Schaff *et al.*, "Low-dose mifepristone 200 mg and vaginal misoprostol for abortion," *Contraception* 1999;59:1-6; Eric A. Schaff *et al.*, "Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days," *Contraception* 2000;61:41-6; Eric A. Schaff *et al.*, "Vaginal misoprostol administered at home after mifepristone (RU486) for abortion," *J Fam Pract* 1997;44:353-60.

⁶⁰ *Id.*; see also Batya Elul *et al.*, "In-depth Interviews with Medical Abortion Clients: Thoughts on the Method and Home Administration of Misoprostol," *JAMA* 2000; 55: 169-72.

⁶¹ Eric A. Schaff *et al.*, "Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days," *Contraception* 2000; Eric A. Schaff *et al.*, "Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion," *Contraception* 2001;64:81-5.

⁶² Mitchell D. Creinin *et al.*, "Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomized trial," *Br J. Obstet Gynaecol* 2001; 108:469-73; Hazem El-Refaei *et al.*, "Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol," *New Engl J Med* 1995; 332:983-7.

⁶³ Signing physicians must attest that they have: (1) the ability to assess the duration of pregnancy accurately; (2) the ability to diagnose ectopic pregnancies; (3) the ability to provide surgery if the patient requires surgery due to an incomplete abortion or severe bleeding (or that the physician has made plans to provide such care through others) and the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation (continued...)

these restrictions forbids alternative evidence-based regimens or requires dispensing according to the regimen described in the labeling. Nor do these restrictions, or the language of the Patient Agreement, preclude physicians from providing information about alternative evidence-based regimens or from having their patients execute additional informed consent forms. The lack of any discussion of evidence-based regimens in the Patient Agreement in no way suggests doctors cannot discuss such regimens with their patients or precludes them from doing so.⁶⁴

As the FDA-approved “Medication Guide” for Mifeprex states, “Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. For more information ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.” More recently, FDA acknowledged, in discussing Mifeprex, that “Because physicians exercise their judgment in prescribing what they feel is best for their patient, they may decide to use an ‘off-label regimen,’ rather than the approved regimen.”⁶⁵ This is consistent with FDA’s historical approach to evidence-based uses. For example, in 1982, FDA stated that the FDCA

and that they have (4) read and understood the prescribing information for Mifeprex attached to the Prescriber Agreement. In addition, by signing the Prescriber Agreement, physicians represent that they will: (1) (a) fully explain the procedure to each patient, (b) give each patient a copy of the Medication Guide and the Patient Agreement, (c) allow each patient to read the Medication Guide and the Patient Agreement, (d) give each patient an opportunity to discuss the Medication Guide and the Patient Agreement, (e) obtain each patient’s signature on a copy of the Patient Agreement, and (f) sign the Patient Agreement; (2) notify Danco in writing in accordance with the *Dosage and Administration* section of Package Insert in the event that a pregnancy is not terminated at the conclusion of the treatment procedure; (3) report all hospitalizations, transfusions, or other serious events to Danco, identifying patient only by package serial number of Mifeprex; and (4) record in each patient’s record the package serial number of Mifeprex administered to the patient.

⁶⁴ Indeed, Mifeprex prescribers must provide information beyond that contained in the Patient Agreement to their patients, either orally or in the form of additional informed consent forms. For instance, the Patient Agreement contains no discussion of alternative methods of abortion. A doctor’s failure to discuss these with his or her patients could be tantamount to failing to obtain informed consent.

⁶⁵ FDA, Dear Doctor Mifeprex Q&A, Apr. 17, 2002, supra n.49.

does not . . . limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature. . . . [A]ccepted medical practice often includes drug use that is not reflected in approved drug labeling.⁶⁶

FDA has not attempted to regulate a clinician's exercise of medical judgment in prescribing approved drugs for alternative evidence-based uses, and such exercise of medical judgment remains appropriate in the prescribing of Mifeprex.

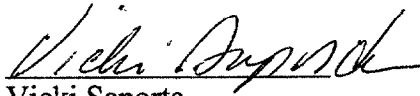
Conclusion

For the reasons set forth above, as well as those set forth in the Population Council and Danco Opposition, the Petitioners set forth no sound scientific basis on which the Mifeprex NDA should be withdrawn. FDA's approval of the Mifeprex NDA achieved an appropriate balance between the need to assure safe and effective use, on the one hand, and the need to avoid unnecessary federal regulation of the practice of medicine, on the other. The scientific data collected since the Mifeprex approval continue to support the drug's safety and effectiveness. Consequently, FDA should promptly deny the Petitioners' requests.

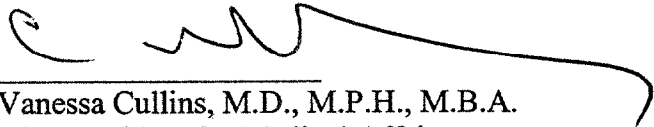
⁶⁶ "Use of Approved Drugs for Unlabeled Indications," 12 FDA Drug Bulletin 4 (April 1982). Similarly, as the preamble to the final rule adopting Subpart H makes clear, that rule "does not itself prevent a physician from prescribing a drug granted accelerated approval for an unapproved use. . . . Physicians may choose to prescribe the drug for a condition not recommended in the labeling." New Drug, Antibiotic, and Biological Drug Product Regulations: Accelerated Approval, 57 Fed. Reg. 58942 (Dec. 11, 1992).

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